REMARKS

The substitute specification is being submitted in response to the request by the Examiner, to ensure legibility and facilitate printing once the Application is passed to issue. A **copy of the marked-up original specification is respectfully submitted herewith in order to confirm same.** No new matter has been added. Accordingly, entry of the substitute specification is respectfully requested.

The Objection

On page 3 of the Office Action, the Examiner has objected to the Sequence Listing, because the content of the computer readable form does not comply with the requirements of 37 C.F.R. § 1.822 and/or 1.823.

Applicants have enclosed a substitute specification, Sequence Listing and corresponding diskette, which corrects those errors denoted in the Raw Sequence Listing Error Report. A computer readable form of the Sequence Listing included with the substitute specification filed herewith is also enclosed. The content of the paper and computer readable copies are the same. 37 C.F.R. § 1.821(f). No new matter has been added. Accordingly, withdrawal of the objection is requested.

The Rejection

Claims 24, 71, 74 and 77-79 have been rejected as non-enabled. The Examiner has contended that the specification does not reasonably provide enablement for other mammalian and human E5-1 proteins. The conclusion is that the claims are enabled only for E5-1 proteins having the sequence of SEQ ID NO:138 (wild-type protein) and SEQ ID NO:138 wherein the Asn at amino acid position 141 has been replaced by Ile and/or wherein

the Met at amino acid position 239 has been replaced by Val (i.e., naturally occurring mutants).

Applicants traverse the rejection. The major premise of the rejection is that E5-1 homologues are not present in other mammalian species because Alzheimer's is a uniquely human disease. The specification teaches that the related human ARMP protein has a homolog in mice. Applicants submit, therefore, that one skilled in the art would not be surprised of the existence of other E5-1 homologs. More importantly, at least two other E5-1 proteins have been reported since the time the claimed invention was made. The sequences of two of these homologs, isolated from the house mouse and Norway rat, are described in the GenBank database, and attached hereto. A comparison of these sequences with the human E5-1 sequence identified as SEQ ID NO:138 clearly shows that the three amino acid sequences have substantial sequence similarity. In fact, the house mouse and Norway rat sequences are about 95% identical to SEQ ID NO:138.

These teachings establish a level of predictability of structure and a correlation between structure and function among the claimed embodiments. More importantly, the regions of sequence similarity include the conserved regions of the human E5-1 protein disclosed on pages 39-40 and Table 8 of the substitute specification. Plainly, the teachings of the present specification would have enabled the identification of other embodiments embraced by the claims, such as the house mouse and Norway rat sequences. Contrary to the allegations made in the Office Action, the specification teaches not only the conserved regions of the human E5-1 protein, but how they

are used, e.g., to generate antibodies or develop cloning strategies for identifying other mammalian E5-1 equivalents. *See* page 28, line 15 to page 29, line 18, and pages 45-48 of the original specification. These teachings would have enabled one skilled in the art to identify homologous E5-1 proteins in other mammalian species without undue experimentation. Accordingly, reconsideration and withdrawal of the rejection are requested.

Applicants also traverse the Examiner's contention that only the specific mutants disclosed in the specification are enabled. Again, based upon Applicants' discovery of the E5-1 gene and protein, their association with early onset familial Alzheimer's Disease, and the teachings of the specification, any naturally occurring mutant E5-1 protein may be identified without undue experimentation. Accordingly, reconsideration and withdrawal of the rejection are requested.

Applicants submit that the present amendment and accompanying remarks serve to place the claims in condition for allowance. An early notice to this effect is earnestly solicited. The Examiner is encouraged to contact the undersigned if she has any questions or requests additional information.

Respectfully submitted,

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